II. REMARKS AND ARGUMENTS

A. Regarding the Amendments

The specification was amended to correct a typographical error in which Fig. 4D was mistakenly referred to as Fig. 4 and to correct a typographical error in which Fig. 4A was mistakenly referred to as Fig. 4. Claims 17-20 were amended by deleting the term non-native

B. Response to Office Action

1. Objections

Claims 17, 18, and 20 were objected due to the inclusion of non-elected subject matter. Applicants acknowledge that the atomic coordinates for the ICL-3-nitropropionate complex, compounds selected by design starting from a known inhibitor, and competitive inhibitors are presently being examined. Applicants acknowledge that the non-elected subject matter has been withdrawn from consideration. Applicants remind the Examiner that the non-elected subject matter should be examined once an allowable generic claim is acknowledged.

The Examiner objected to the specification because Figure 4D was not briefly described. The present amendment corrects a typographical error in which Fig. 4D was mistakenly typed at Fig. 4. The present amendment obviates this objection.

The Examiner objected to the title of the invention, alleging that the title is not descriptive because it cited a structure and inhibitory agents, which the Examiner alleges are not claimed in the elected invention. Applicants will amend the title of the invention as appropriate once allowable subject matter has been acknowledged.

C. Rejections under 35 U.S.C. § 112

Claims 17-20, 23-30, and 32-34 have been rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter regarded by Applicants as the invention. Specifically, the Examiner alleges that the term "non-native" in claims 17, 18, 19, and 20 is vague and indefinite because it is unclear what criteria are being used to determine that a substrate is non-native. The Examiner specifically alleges that this term causes confusion because one of skill in the art might interpret non-native to refer to a compound that is from a different county than the microbe. Applicants submit that the term "non-native" is widely used in the art to describe compounds that are not naturally occurring within an organism and that one of skill in the art would not be confused by the use of the term in the claims. However, Applicants have removed the term from the claims by the present amendment so as to facilitate allowance of the claims. Applicants stress that this is not a narrowing amendment.

D. Rejections under 35 U.S.C. § 103

Claims 17-20, 23-30, and 32-34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,856,116 A, by Wilson et al., in view of In re Gulack, 703 F.2d 1381 (Fed. Cir. 1983) and in view of "The Crystal Structure and Active Site Location of Isocitrate Lyase from the Fungus Aspergillus Nidulan" *Structure* (2000) 349-62, by Britton, et al. in combination with U.S. Patent No. 6,387,694 B1, by McKinney et al. Specifically, the Examiner alleges that Wilson discloses a method for identifying inhibitors by having the inhibitor bind to the active site of interleukin-1 beta converting enzyme (ICE), as defined by the structural coordinates of ICE. The Examiner alleges that even though the method disclosed by Wilson does not specify the atomic coordinates of the present invention, the atomic coordinate

data do not distinguish the invention from the prior art because they are descriptive nonfunctional subject matter. The Examiner alleges that In re Gulack defines nonfunctional descriptive material as descriptive material that is not functionally related to the substrate. The Examiner alleges that in the instant case, the atomic coordinates and data are merely stored so as to be read or outputted by a computer without creating any functional interrelationship, either as part of the stored data or as part of the computing processes performed by the computer and therefore does not impart functionality either to the data or to the computer. The Examiner alleges that Britton discloses the crystal structure and active site location of isocitrate lyase from the fungus *Aspergillus nidulans* and nitroproprionate and itaconate as inhibitors of ICL from mycobacteria for controlling growth of the mycobacteria. The Examiner alleges that McKinney discloses the use the atomic coordinates produced from M. tuberculosis ICL for identifying ICL inhibitors. The Examiner alleges that it would have been obvious to improve the method of Wilson to design inhibitors to ICL as taught by Britton and McKinney. The Examiner alleges that the crystal structure data of the claims does not distinguish the invention from the prior art. Applicants respectfully traverse.

Wilson et al. is directed to the crystal structure of interleukin-1b converting enzyme (ICE) and does not concern the crystal structure of isocitrate lyase enzyme. Though Wilson discusses techniques to design, select and synthesize inhibitory compounds for binding the active site of ICE, this discussion is specific to ICE because the only crystal structure data disclosed by Wilson is that of ICE. For one of skill in the art to design inhibitors for isocitrate lyase enzyme, as in the present invention, one would require the crystal structure data for microbial isocitrate lyase enzyme. Wilson does not provide such data.

Britton et al. concerns the crystal structure and active site location of isocitrate lyase from the fungus Aspergillus nidulans. However, the structures discussed by Britton are disordered in the active cite region. *See*, p. 350 and p. 354. The Britton structures therefore have little utility for drug design. The Examiner stated that Britton also discloses nitroproprionate and itaconate as inhibitor of ICL, as in claims 26, 28, and 34. While it is true that Britton does mention these inhibitors, this fact does not impact claims 26, 28, and 34 because these claims are directed to a method of identifying an inhibitor, as recited in independent claim 20. The presence in the art of known inhibitors does not impact a novel method of identifying previously unknown inhibitors.

McKinney et al. is directed to polynucleic acids encoding mycobacterial isocitrate lyase, mutated forms of the nucleic acids, and to isolated proteins encoded by the polynucleic acids. The Examiner alleges that McKinney discloses the use of atomic coordinates produced from M. tuberulosis isocitrate lyase for identifying inhibitors. McKinney does not provide enough information to actually identify inhibitors. As McKinney points out, knowledge of the three dimensional crystal structure would be required to achieve such structure-based rational design of inhibitors and McKinney does not provide the crystal structure. McKinney, in fact, recognizes a need in the art for the structural data for ICL and the present invention fulfills this need.

The Examiner has acknowledged that the prior art does not disclose the crystal structure coordinates of the present invention. It is exactly these coordinates that allow one of skill in the art to practice the present invention and rationally design and/or identify inhibitors for the microbial ICL enzyme. None the less, the Examiner refuses to lend any weight to the crystal structure coordinates, citing In re Gulack for the proposition that the coordinates are "non-functional descriptive material" and therefore do not lend patentable weight to the claims.

In re Gulack concerns the patentable weight afforded to printed matter, and has nothing to do with structural coordinate data. In re Gulack is a Court of Appeals, Federal Circuit decision from 1983, regarding the Patent and Trademark Office Board of Appeals' rejection of an invention for displaying a particular sequence of digits on the outside surface of a band. The Board sustained the Examiner's rejection of the claims as being obvious given prior art teachings of similar bands not having numbers. The Board argued that printed matter cannot impart a patentable feature to a claim. The Board stated that there was no functional relationship between the printed matter and substrate, i.e., the band. The Federal Circuit reversed, clarifying that a functional relationship to size or to type of substrate or to conveying information about the substrate is not required, rather, what is required is the existence of differences between the appealed claims and the prior art sufficient to establish patentability. The Court stated that a new and unobvious functional relationship between the printed matter and the substrate is required. The Examiner interprets this as meaning that novel structural data that is read or used by a known computer methodology does not impart functionality either to the data as structured or to the computer, and therefore does not contribute to the patentability of claims that recite this data.

The Examiner's analysis is simply not applicable to the presently pending claims. Applicants are not claiming a new algorithm or device for identifying inhibitors in general. Rather, Applicants claim a method of identifying inhibitors or compounds to bind to specific proteins, and the method of identifying such inhibitors or compounds rely on the structural coordinates that Applicants have discovered. Such inhibitors and agents are potentially important for combating infection by known pathogens. The art recognizes the need for such a method, but does not provide the structural coordinates that are required for its realization.

The Examiner seems to consider the fact that the art recognizes the need for such a method as an indication that the method is obvious. For example, the Examiner states "An artisan of ordinary skill in the art would have been motivated to partake the concept emphasized by Wilson et al. and improve on the method by using the method of Wilson et al. for designing inhibitors to isocitrate lyase as taught by Britton et al. and McKinney et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to use the method of designing inhibitors to isocitrate lyase as taught by Wilson et al., Britton et al., and McKinney et al." However, regardless of how motivated one of skill in the art might have been, it would have been impossible for him to design such inhibitors without having the structural coordinates that are provided by the present invention. The prior art (McKinney) recognizes this fact.

The structural coordinates provided by the present invention are not easily obtained. Jan Drenth, on p. 16 of Principles of Protein X-ray Crystallography, referenced by the Examiner, states, "Protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable." The Britton reference is further evidence of this fact, because in spite of the work described therein, the structural data obtain is unsuitable for rational drug design.

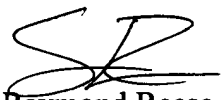
The interpretation of In re Gulack proposed by the Examiner does not comport with the fundamental purpose of the patent system, which is to promote the progress of science and useful arts by securing for a limited time the exclusive right of inventors to their discoveries. In the context of the present invention, the patent system should encourage inventors to invest the effort required to discover the structures of proteins that the art recognizes will lead to useful drug discoveries. Contrarily, under the Examiner's interpretation, this recognition in the art of the

usefulness of such structures would render such inventions as obvious, and therefore discourage inventors from investing the effort to elucidate these structures.

The prior art recognizes the need for the structures disclosed in the instant application but does not teach the structures. The references state that the art of obtaining such structures is unpredictable. Applicants therefore submit that the present invention is not obvious, in light of the cited references and respectfully request that the rejection under U.S.C. 103 be withdrawn.

The Examiner is invited to contact the undersigned patent agent at 713-787-1558 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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